Interpreting signals from the peripheral nerve in amyloidosis: a call for action

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How to cite this article: Verriello L, Dalla Torre C, Pauletto G, Gigli GL. Interpreting signals from the peripheral nerve in amyloidosis: a call for action. Vessel Plus 2021;5:51. https://dx.doi.org/10.20517/2574-1209.2021.69

Received: 30 Apr 2021 First Decision: 15 Jun 2021 Revised: 30 Jun 2021 Accepted: 21 Jul 2021 First online: 21 Jul 2021

Abstract

Systemic amyloidosis includes a group of disorders, characterized by deposition of insoluble aggregates of amyloid fibrils in various tissues that lead to disruption of normal tissue structure and impaired function. They are currently categorized as hereditary and secondary. Peripheral neuropathy is a frequent complication of systemic amyloidosis. The most common phenotype is a length-dependent sensorimotor polyneuropathy with autonomic dysfunction, but there are many atypical presentations that often lead to delayed diagnosis. In this review, we emphasize the neurological clinical aspects that induce a suspicion of amyloidosis, the possible differential diagnosis and the diagnostic pitfalls. An early diagnosis of the disease is crucial for rapid initiation of appropriate treatment that may change the course and the progression of the disease.

Keywords: Amyloidosis, neuropathy, transthyretin

INTRODUCTION

Systemic amyloidosis includes a heterogeneous group of disorders, characterized by the accumulation of amyloid fibrils in different tissues, leading to structure disruption and impaired function.
All amyloid fibril proteins are called protein A plus an abbreviated form of the precursor protein name as a suffix. Therefore, amyloid fibrils protein AL comes from immunoglobulin light chains and the disease is known as AL amyloidosis, while TTR stands for transthyretin and the disease is ATTR amyloidosis. Further details can be reported after the protein name, for instance ATTRwt or ATTRv (wt: wild-type and v: variant). Moreover, the specific mutation can replace the “v”, e.g., ATTRV30M (p. TTRV50M)\(^2\).

Many organs/systems may be affected by systemic amyloidosis, including heart, kidneys, liver, gastrointestinal tract, and nervous system. Peripheral neuropathy is among the most frequent complications. Its clinical presentation varies according to the affected nerves and their level of structural involvement\(^3\-^5\).

The most common phenotype is a length-dependent sensorimotor polyneuropathy, but there are many atypical presentations that often lead to delayed diagnosis\(^5\).

In this review, we describe the clinical features of neuropathy in hereditary and acquired forms of amyloidosis, emphasizing the clinical aspects that should induce the clinicians to consider amyloidosis in their differential diagnosis.

**INHERITED FORMS OF AMYLOID NEUROPATHY**

Hereditary amyloid neuropathy includes a group of autosomal dominant diseases, due to extracellular accumulation of variant proteins, damaging somatic and autonomic peripheral nervous fibers.

The most common hereditary form of amyloid neuropathy is ATTR amyloidosis\(^3\).

Other mutated proteins, like gelsolin and apolipoprotein A, may lead to amyloid neuropathy whose specific clinical characteristics are summarized in Table 1.

**Hereditary transthyretin amyloidosis**

Hereditary transthyretin amyloidosis (ATTRv) is an autosomal dominant disease, due to a mutation in transthyretin (TTR) gene, located on chromosome 18\(^6\). TTR is responsible for the transport of thyroxin and retinol binding protein complex. TTR consists of a tetrameric protein with four identical subunits, and it is primarily synthesized by the liver. Point mutations induce destabilization and dissociation of the TTR tetramer into monomers, which aggregate into amyloid fibrils in different organs at the extracellular level\(^6\).

Some mutations are associated predominantly with peripheral and autonomic neuropathy, others with prevalent cardiomyopathy. Finally, there are mutations causing a mixed phenotype\(^7\).

**Clinical features**

ATTRv amyloidosis with polyneuropathy phenotype depends on geographic location, causative gene mutation, and age of onset. Moreover, for each specific mutation in the TTR gene, the phenotype may be various, even within the same family.

In endemic areas (e.g., Portugal, Sweden, Japan, and Brazil), the most frequent phenotype is a length-dependent small-fibers polyneuropathy with dysautonomia\(^8\-^9\).
Table 1. Inherited amyloid neuropathies and their clinical features

<table>
<thead>
<tr>
<th>Type of amyloidosis</th>
<th>Underlying mutation</th>
<th>Precursor protein</th>
<th>Main clinical features</th>
</tr>
</thead>
<tbody>
<tr>
<td>ATTRv</td>
<td>Mutations in TTR gene</td>
<td>Abnormal TTR</td>
<td>Length-dependent sensory-motor axonal polyneuropathy with dysautonomia</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Rapidly progressive and disabling axonal polyneuropathy in the elderly</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Chronic inflammatory demyelinating polyneuropathy like (CIDP-like)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Multifocal neuropathy with onset at upper limbs</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Ataxic phenotype</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Motor neuropathy</td>
</tr>
<tr>
<td>AApoA1</td>
<td>Mutations in apolipoprotein gene</td>
<td>Abnormal ApoA1</td>
<td>The disease affects mainly kidneys, liver, and gastrointestinal tract</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Gly26Arg mutation may cause a length-dependent polyneuropathy</td>
</tr>
<tr>
<td>Agel</td>
<td>Mutations in gelsolin gene</td>
<td>Abnormal gelsolin</td>
<td>Cranial and peripheral neuropathy; cutis laxa and corneal lattice dystrophy</td>
</tr>
</tbody>
</table>

Onset symptoms generally include sensory abnormalities due to damage of small fibers, such as numbness, burning sensation and allodynia in the feet that often worsen at night. Neurological assessment reveals predominant loss of thermal sensation and nociception.

With the progression of the disease, large sensory and motor nerve fibers are involved, inducing weakness and reduction of vibration sense and proprioception. Furthermore, symptoms gradually spread from the distal extremities to proximal lower limbs and upper limbs\[9\].

Given the involvement of small fibers, patients commonly present with autonomic dysfunctions\[10\].

Cardiovascular autonomic neuropathy may induce orthostatic hypotension and life-threatening arrhythmias. Patients with orthostatic hypotension may complain of light-headedness, blurred vision, and dizziness when standing.

Gastrointestinal autonomic symptoms, due to gastroparesis and dysmotility, include alternating post-prandial diarrhea, severe constipation, early satiety, and crisis of vomiting.

Regarding genitourinary tracts, in the early stage of the disease, impairment of sacral parasympathetic fibers may result in alteration of bladder sensation, urine retention, dysuria, and incomplete bladder emptying. Then, when the motor sympathetic and somatic nerves are involved, urgency up to overflow incontinence appears. In males, erectile dysfunction is the earliest finding.

There are over 100 TTR mutations that cause ATTRv, but not all of them determine the characteristic clinical picture of ATTRv amyloidosis with polyneuropathy. The most common one is a point mutation that leads to the substitution of methionine for valine at position 30 (Val30Met)\[11\]. By the age at onset, patients with Val30Met mutation are classified into two groups: early onset (< 50 years) and late onset (> 50 years).

Early onset ATTRV30M patients are seen in the endemic areas and they are characterized by onset before 50 years, high penetrance rate and classical clinical presentation, that is small fibers polyneuropathy with marked autonomic dysfunction\[12\].
On the other hand, late-onset Val30Met patients are seen in non-endemic areas, with onset after 50 years, low penetrance rate, male predominance, and no family history. Clinically, they show sensorimotor symptoms, beginning in the distal lower extremities, with loss of all sensory modalities and mild autonomic dysfunction. In late-onset ATTRV30M, amyloid cardiomyopathy is frequently encountered[^8,^9].

Carpal tunnel syndrome (CTS) is often seen in ATTRv amyloidosis with polyneuropathy, caused by the focal amyloid deposit in the transverse carpal ligament.

In recent case series, CTS occurred in two-thirds of patients with neuropathy related to ATTRv and, frequently, preceded the diagnosis by a decade[^12,^13].

The main symptoms of CTS are numbness, tingling, and pain in the fingers, especially the thumb, the index, and the middle fingers. At onset, these symptoms often wake up the patient from sleep, then the numbness may become constant over time. At the later stage, the patient may experience grip weakness.

Although CTS is commonly found in the general population, it tends to be bilateral, asynchronous and more severe in patients with ATTRv amyloidosis with polyneuropathy than in subjects with idiopathic CTS.

Moreover, some specific TTR mutations, such as Leu58Arg[^14], Ile84Ser[^15], and Tyr114His[^16], can present with CTS as the only neurological manifestation in addition to other systemic symptoms.

Patients with ATTRv and atypical phenotypes of neuropathy have been described in non-endemic areas. They are all late-onset cases and their clinical presentation includes: length-dependent all-fiber sensorimotor polyneuropathy mimicking chronic inflammatory demyelinating polyneuropathy (CIDP)[^17-^19], multifocal neuropathy with onset in upper limbs[^20], ataxic phenotype[^21], and motor neuropathy[^22,^23]. This clinical heterogeneity may frequently cause misdiagnosis.

One of the most frequent misdiagnoses of ATTRv amyloidosis with polyneuropathy is CIDP[^17-^19,^24-^27]. The main factors leading to this misdiagnosis, in sporadic late-onset ATTRv amyloidosis with polyneuropathy, are demyelinating features on nerve conduction study and mild elevation of cerebrospinal fluid (CSF) proteins. However, patients with ATTRv amyloidosis with polyneuropathy frequently present severe pain not restricted to lower limbs, while in case of CIDP, pain is rare and mild or moderate. Furthermore, dysautonomic features are not a distinctive characteristic of CIDP and they provide a clue toward the diagnosis of ATTRv amyloidosis with polyneuropathy, although they are less common in late-onset forms. Thus, pain and dysautonomia, in patients with demyelinating polyneuropathy not responding to immune therapy, are predictors of demyelinating ATTRv amyloidosis with polyneuropathy[^19,^24].

Another atypical phenotype, in non-endemic area, is represented by multifocal neuropathy with onset in upper limbs[^20]. Therefore, it is important to propose early molecular analysis of TTR gene in patients with idiopathic upper limb neuropathies.

Ataxic phenotype, with a rapid course and sensory loss involving mainly vibration and joint position, has been reported in France and Germany associated with Tyr77Ser mutation[^21,^26].

Finally, predominantly motor neuropathies have been described in association with different mutations[^22,^24-^31]. In these cases, bulbar signs (dysarthria, dysphagia, and tongue atrophy) may be encountered, mimicking amyotrophic lateral sclerosis[^23,^26].
Diagnostic pitfalls and red flags

ATTRv amyloidosis with polyneuropathy is frequently diagnosed late, due to variable clinical presentations that make the disease difficult to recognize.

Age at onset may vary, with a wide range from 20 to 80 years. Moreover, incomplete penetrance may be responsible for cases without a positive family history.

Sporadic ATTRv amyloidosis with polyneuropathy is a diagnostic challenge. Some of the most frequent misdiagnosis are: CIDP, idiopathic polyneuropathy, AL amyloidosis, diabetic neuropathy motor neuron disease, and lumbar spinal stenosis [Table 2]. However, lumbar spinal stenosis, due to amyloid deposits within the ligamentum flavum, may be an early manifestation of systemic ATTRv amyloidosis.[33]

Some patients can have significant slowing of motor conduction velocity and sometimes fulfill EFNS/PNS criteria for a definite CIDP. Furthermore, increased protein levels in CSF and negative biopsy contribute to misdiagnosis.[17-19]

The sensitivity of tissue biopsy may be different within the various mutations and the sural nerve biopsy may be unexpectedly negative as the deposition is often sporadic and random.[34,35]

Within the CIDP scenario, fast disease progression and immunomodulatory treatment failure are signs that should suggest an alternative diagnosis, including ATTRv amyloidosis with polyneuropathy.

In the literature, patients with TTR-related amyloidosis who were diagnosed as affected by AL amyloidosis have been described,[36,37] due to the concomitant presence of monoclonal gammopathy or mistakes in immuno-labeling of amyloid aggregates.

This erroneous diagnosis may lead to inappropriate chemotherapeutic treatments; thus, the correct identification of the amyloid precursor is mandatory.

Family history and multi-organ involvement are clues that should raise the clinical suspicion of ATTRv amyloidosis with polyneuropathy.

Considering all available literature and expert opinions, ATTRv amyloidosis with polyneuropathy should be suspected in case of a progressive sensory motor neuropathy associated with at least one of the following “red flags”: family history of neuropathy, early autonomic dysfunctions (e.g., erectile dysfunction or postural hypotension), weight loss not otherwise explained, bilateral CTS, cardiac signs and symptoms (e.g., heart hypertrophy, arrhythmias, cardiomyopathy, or ventricular blocks), renal impairment (e.g., albuminuria), and vitreous opacities.[38][Figure 1]

Early diagnosis of ATTRv amyloidosis with polyneuropathy is important, considering currently available therapies. The main investigation is the genetic test, by mean of the TTR gene sequencing to search for amyloidogenic variants. Biopsy (e.g., salivary glands, sural nerve, or abdominal fat) allows detecting and typing of the amyloid in the tissue.

Once the diagnosis has been made, assessing disease severity and monitoring its progression are crucial to establish the indication for treatment.
Table 2. Mimics of ATTRv amyloidosis with polyneuropathy, diagnostic pitfalls, and red flags

<table>
<thead>
<tr>
<th>Mimics</th>
<th>Diagnostic pitfalls</th>
<th>Red flags</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chronic axonal idiopathic polyneuropathy</td>
<td>Axonal PN in the elderly who seems idiopathic</td>
<td>Rapidly progressive and disabling</td>
</tr>
<tr>
<td>CIDP</td>
<td>Decreased NCV</td>
<td>Difficulties in walking</td>
</tr>
<tr>
<td>Lumbar spinal stenosis</td>
<td>Albuminocytologic dissociation</td>
<td>Pain</td>
</tr>
<tr>
<td>AL amyloidosis</td>
<td>Negative tissue biopsy</td>
<td>Dysautonomia</td>
</tr>
<tr>
<td>Diabetic neuropathy</td>
<td>Progressive walking difficulties</td>
<td>No response to immunotherapy</td>
</tr>
<tr>
<td>Motor neuron disease</td>
<td>Occurrence of monoclonal gammopathy</td>
<td>Worsening despite of surgery</td>
</tr>
<tr>
<td></td>
<td>False immunolabeling of amyloid deposits</td>
<td>Abnormal NCS</td>
</tr>
<tr>
<td></td>
<td>Length-dependent PN with involvement of small fibers</td>
<td>Rapidly progressive</td>
</tr>
<tr>
<td></td>
<td>Dysautonomia</td>
<td>Difficulties in walking</td>
</tr>
<tr>
<td></td>
<td>Bulbar signs (tongue atrophy, dysarthria, and dysphagia)</td>
<td>No symptoms and signs of upper motor neuron involvement</td>
</tr>
</tbody>
</table>

PN: Polyneuropathy; CIDP: chronic inflammatory demyelinating polyneuropathy; NCS: nerve conduction velocity.

Several scales can be used for the assessment. The main one is the Coutinho staging system that classifies ATTRv amyloidosis with polyneuropathy into three stages, from 0 (asymptomatic) to 3 (patient confined to wheelchair)\textsuperscript{[39]} [Table 3].

Dysautonomic involvement can be assessed by administering the Composite Autonomic Symptom score 31 (COMPASS 31)\textsuperscript{[40]}, a self-reported questionnaire.

**Apolipoprotein A1-related amyloidosis**

Apolipoprotein A1 is a protein released by the liver and the small intestine. It represents the major constituent of high-density lipoproteins and plays a role in reverse cholesterol transport.

Hereditary amyloidosis with mutation of apolipoprotein A1 is rarely encountered.

The disease typically begins around 40 years and affects mainly the liver, gastrointestinal tract, and kidneys, frequently inducing organ failure.

There are sixteen already-discovered mutations of apo-A1 gene. Among them, Gly26Arg mutation may induce a length dependent polyneuropathy\textsuperscript{[41]}.

**Gelsolin-related amyloidosis**

The so-called Finnish type amyloidosis or hereditary gelsolin amyloidosis is a rare autosomal dominant disorder.

Generally, the disease begins around 30 years of age, with various clinical features, including cranial and peripheral neuropathy, *cutis laxa*, and corneal lattice dystrophy, variably associated with systemic symptoms\textsuperscript{[42]}. 

Figure 1. Clues for diagnosis of ATTRv amyloidosis with polyneuropathy in patients with chronic peripheral neuropathy.
Table 3. Severity of ATTRv amyloidosis with polyneuropathy, measured by Coutinho FAP stage

<table>
<thead>
<tr>
<th>Stage</th>
<th>FAP stage</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>Asymptomatic</td>
</tr>
<tr>
<td>I</td>
<td>Walking is autonomous with mild distal symptoms to lower limbs</td>
</tr>
<tr>
<td>II</td>
<td>Walking is possible only with one or two supports</td>
</tr>
<tr>
<td>III</td>
<td>Walking is not possible. Patient confined to wheelchair/bed</td>
</tr>
</tbody>
</table>

FAP: Familial amyloid polyneuropathy.

Cranial neuropathy is the main neurological manifestation, presenting with facial nerve palsy and trigeminal neuropathy. Later, lower cranial nerves, such as hypoglossal, glossopharyngeal, and vagal nerves, are involved, resulting in bulbar palsy. After the age of 40-50 years, patients develop a length-dependent sensorimotor peripheral neuropathy, sometimes with mild autonomic dysfunction[42-44].

**ACQUIRED FORMS OF AMYLOID NEUROPATHY**

Acquired forms of amyloid neuropathy are caused by the misfolding of monoclonal k or λ light chains in the primary systemic form (AL), serum amyloid A protein in the secondary form (AA), and beta-2 microglobulin (B2M) in dialysis-associated amyloidosis [Table 4].

**AL amyloidosis**

The incidence of AL amyloidosis is approximately 12 cases per million persons per years; there is an estimate prevalence of 30,000 to 45,000 cases in the European Union and the United States[45,46]. It consists of a multisystem disease where amyloid fibrils, made of monoclonal immunoglobulins light chains, are deposited in many tissues. The organs usually involved are: kidney (74%), heart (60%), liver (27%), peripheral (22%), and autonomic nervous system (18%)[47]. If not treated, the prognosis of AL amyloidosis is unfavorable.

The majority of patients are middle aged to elderly males, who present with symptoms and signs including: congestive heart failure, cardiac arrhythmias, peripheral edema, orthostatic hypotension, weight loss, diarrhea, abdominal pain, purpura, nephrotic syndrome, hepatomegaly, renal failure, macroglossia, CTS, and neuropathy[3].

Up to 35% of patients with AL amyloidosis develop peripheral neuropathy[48]. It usually starts by affecting small fibers, with distal and symmetric distribution. When large fibers become affected, patients develop numbness, tactile hypoesthesia, and hypopallesthesia. As the disease progresses, loss of strength and autonomic dysfunctions may occur. Among the latter, orthostatic hypotension is the main symptom[39], but urinary retention, fecal incontinence, and erectile dysfunction can also be observed. Over time, symptoms can progress requiring orthopedic appliance and wheelchair. Electrophysiological examination discloses an axonal length-dependent polyneuropathy[48].

CTS occurs in up to 21% of patients[49]. In 7%-17% of cases[49], peripheral neuropathy is the first clinical sign and it may precede the diagnosis of amyloidosis AL by up to 48 months, which can result in misdiagnosing of idiopathic neuropathy.

As in the case of ATTRv, patients with AL amyloidosis may present atypical manifestations, such as: mono- or multi-cranial neuropathy, mononeuropathies, multiplex mononeuritis, motor neuron diseases, and demyelinating polyradiculoneuropathies[50]. Particularly, different cases of demyelinating neuropathies have
Table 4. Acquired amyloid neuropathies and main clinical features

<table>
<thead>
<tr>
<th>Type of amyloidosis</th>
<th>Precursor protein</th>
<th>Organs involved</th>
<th>Clinical picture of neuropathy</th>
</tr>
</thead>
<tbody>
<tr>
<td>AL</td>
<td>k or λ light chains</td>
<td>Kidney (74%), Heart (60%), Liver (27%), Peripheral nervous system (22%)</td>
<td>Length-dependent symmetric sensori-motor axonal polyneuropathy, with autonomic manifestation, Carpal tunnel syndrome, Atypical manifestation: mono or multicranial neuropathy, mononeuropathies, multiplex mononeuritis, motor neuron diseases, demyelinating polyradiculoneuropathy</td>
</tr>
<tr>
<td>AA</td>
<td>Serum amyloid A protein</td>
<td>Kidney, Neurological manifestation (rare)</td>
<td>Peripheral autonomic neuropathy</td>
</tr>
<tr>
<td>Beta2-microglobulin</td>
<td>β2-protein</td>
<td>Kidney, Peripheral nervous system</td>
<td>Carpal tunnel syndrome, Autonomic neuropathy</td>
</tr>
</tbody>
</table>

been described, associated with elevated CFS protein concentration and nerve root enhancement and enlargement at MRI examination, according to definite CIDP for EFNS/PNS criteria\[^{50,51}\]. However, differently from CIDP patients, subjects affected by AL amyloidosis have prominent autonomic symptoms.

Another important hallmark for AL amyloidosis is CTS, especially if bilateral, which is associated with peripheral neuropathy. The finding of monoclonal protein associated with axonal neuropathy should induce the suspicion of AL amyloidosis.

Monoclonal protein includes IgG, IgM, IgA, or light chains only\[^{52}\]. In 10% of all cases, however, a monoclonal protein is not found\[^{53}\]. Tissue biopsy (e.g., abdominal fat and sural nerve) should be performed when AL amyloidosis is highly suspected.

In conclusion, the triad composed by “autonomic features, CTS, and monoclonal proteins” associated with peripheral neuropathy are the hallmark that should suggest AL amyloidosis diagnosis. Amyloid deposits in biopsied tissue confirm the diagnosis.

**AA amyloidosis**

AA amyloidosis is a systemic disease that can develop as a complication of various chronic inflammatory disorders. Some studies identify obesity and age as predisposing factors\[^{54}\]. The amyloid fibrils are composed of aggregation of serum amyloid A, an acute phase protein, produced by the liver. The kidney is the organ principally involved. Neurological manifestations are rare, even if cases of peripheral autonomic neuropathy have been reported\[^{55}\].

**B2M associated amyloidosis**

B2M associated amyloidosis has been described in patients with chronic kidney disease on long-term hemodialysis. It is characterized by the accumulation of amyloid fibrils of B2M in the *flexor retinaculum*, leading to CTS\[^{56}\], in the bones and the joints, causing chronic arthropathy and bone lesions.

A genetic autosomal dominant form has also been described with Asp76Asn variant B2M, characterized by progressive gastrointestinal symptoms and autonomic neuropathy. In this case, patients have normal renal function and normal circulating B2M values, suggesting the fibrilligenicity of the protein in physiological conditions\[^{57}\].
CONCLUSIONS
Peripheral neuropathy is a common feature of hereditary and acquired forms of amyloidosis, with considerable heterogeneity in the clinical manifestation.

The most common phenotype is a progressive length-dependent sensorimotor polyneuropathy with autonomic dysfunction. However, there are many atypical presentations that often lead to delayed diagnosis.

The prevalent type of hereditary amyloid neuropathy is represented by ATTRv amyloidosis with polyneuropathy. In non-endemic areas, 52%-77% of cases do not show a positive family history and clinical presentation of the disease is variable. Thus, diagnosis of ATTRv amyloidosis with polyneuropathy may be missed and multiple misdiagnoses have been reported.

Often, sporadic cases may be misdiagnosed as CIDP, idiopathic axonal polyneuropathy, AL amyloidosis, diabetic neuropathy, or lumbar spinal stenosis.

Subjects with progressively disabling polyneuropathy and one or more red flag symptoms suggestive of multisystem involvement should be screened for ATTRv amyloidosis with polyneuropathy.

Early diagnosis of amyloid neuropathy allows rapid initiation of appropriate treatment that may change the course and the progression of the disease.

DECLARATIONS
Authors’ contributions
Designed the review, performed all reviewing activities and drafted the manuscript: Verriello L, Dalla Torre C, Pauletto G
Supervised all reviewing activities and provided critical contributions to the manuscript: Gigli GL
All authors approved the final version of the manuscript.

Availability of data and materials
Not applicable.

Financial support and sponsorship
None.

Conflicts of interest
All authors declared that there are no conflicts of interest.

Ethical approval and consent to participate
Not applicable.

Consent for publication
Not applicable.

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